Parameter Identification in a Respiratory Control System Model

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Abstract

In this paper we study parameter identification issues by computational means for a set of nonlinear delay equations which have been proposed to model the dynamics of a simplified version of the respiratory control system. We design specific inputs for our system to produce “information rich” output data needed to determine values of unknown parameters. We also consider the effects of noisy measurements in the identification process. Several case studies are included.

Introduction

- Mathematical models describing the chemical balance mechanism of the respiratory control system are given in the form of nonlinear, parameter dependent, delay differential equations.
- The analysis of the direct problem shows that the system has a unique equilibrium, and that the stability of this equilibrium depends on the parameter values.
- We present a computational procedure which can be used to perform parameter estimation in respiratory control models. We also illustrate how information rich data can enhance the effectiveness of the estimation process.
- Another issue we study is what are the most promising measurements available for identification purposes?

Model Equations

We consider the system of nonlinear delay equations describing a simple model of the human respiratory control system

$$\dot{x}(t) = a - bx(t) - cV(t, x(t-\tau), y(t-\tau))(x(t) - x_I)$$

$$\dot{y}(t) = -d - ey(t) + fV(t, x(t-\tau), y(t-\tau))(y_I - y(t))$$

where $x(t)$ and $y(t)$ denote the arterial CO_2 and O_2 concentrations, respectively, $V(\cdot, \cdot, \cdot)$ is the ventilation function, τ is the transport delay, x_I and y_I are inspired CO_2 and O_2 concentrations.

Ventilation Function

We assume that the ventilation function has the form

$$V(t, x, y) = G_P(t)W(x, y) \tag{0.1}$$

where the control gain, $G_P(t)$, is piecewise constant

$$G_P(t) = \begin{cases} G_{P1}, & 0 \le t < \theta_1, \\ G_{P2}, & \theta_1 \le t < \theta_2, \\ G_{P3}, & \theta_2 \le t. \end{cases}$$

W is given by

$$W(x, y) = e^{-0.05y}(x - I_P).$$

Coefficients

$$a = 863\frac{\dot{Q}K_{CO_2}P_{V_{CO_2}}}{M_{L_{CO2}}}$$

$$b = 863\frac{\dot{Q}K_{CO_2}}{M_{L_{CO2}}}, c = \frac{E_F}{M_{L_{CO_2}}}$$

$$d = 863\frac{\dot{Q}}{M_{L_{O2}}}(-m_v P_{V_{O_2}} + B_a - B_v)$$

$$e = 863\frac{\dot{Q}m_a}{M_{L_{O_2}}}, f = \frac{E_F}{M_{L_{O_2}}}$$

Parameter Values

τ	min	0.1417
$\dot{Q}$	l/min	6.0
K_{CO_2}		0.0057
$P_{V_{CO_2}}$	mmHg	46.0
$P_{V_{O_2}}$	mmHg	41.0
$M_{L_{CO_2}}$	l	3.2
$M_{L_{O_2}}$	l	2.5
m_v, m_a		0.0021,0.00025
B_v, B_a		0.0662,0.1728
G_{P1}	l/min/mmHg	45.0
I_P	mmHg	35.0
x_I, y_I		0,146.0

Model Equations

Substitution of the normal values into the model equations yields

$$a = 422.4277,\ b = 9.2233,\ c = 0.21875,$$

$$d = 42.8946,\ e = 0.5178,\ f = 0.28,$$

with ventilation function

$$V(t, x, y) = G_P(t)e^{-0.05y}(x - 35),$$

Numerical Approximation

In this section we describe a simple numerical scheme to approximate solutions of the model equations. Let h be a fixed positive constant, and define the notation

$$[t]_h = \left[\frac{t}{h}\right]h,$$

where $[\cdot]$ is the greatest integer function. Then $[t]_h$, as a function of t, is piecewise constant, since $[t]_h = nh$ for $t \in [nh, (n+1)h)$.

Numerical Approximation

For a fixed $h > 0$ we associate the system

$$\dot{x}_h(t) = a - bx_h([t]_h)$$

$$-cV([t]_h, x_h([t]_h - [\tau]_h), y_h([t]_h - [\tau]_h))(x_h([t]_h) - x_I)$$

$$\dot{y}_h(t) = -d - ey_h([t]_h)$$

$$+fV([t]_h, x_h([t]_h - [\tau]_h), y_h([t]_h - [\tau]_h))(y_I - y_h([t]_h))$$

to the model equations for $t \geq 0$.

Numerical Approximation

The solution x_h and y_h of is defined as continuous functions, which are differentiable and satisfy the approximate system on each interval $(nh,(n+1)h)$ $(n = 0, 1, 2, \ldots)$. Since the right-hand-side of the approximating equations are constant on each interval $[nh,(n+1)h)$, we get that both x_h and y_h are piecewise linear continuous functions (linear spline functions). Therefore, they are determined by their values at the mesh points nh.

Numerical Approximations

Introduce the sequences

$$u_n = x_h(nh) \quad \text{and} \quad v_n = y_h(nh),$$

and let

$$k = \left[\frac{\tau}{h}\right].$$

Then integrating the approximating equations from nh to t and taking the limit $t \to (n+1)h-$, we get by simple calculation that u_n and v_n satisfy

$$u_{n+1} = u_n + h(a - bu_n - cV(nh, u_{n-k}, v_{n-k})(u_n - x_I))$$

$$v_{n+1} = v_n + h(-d - ev_n + fV(nh, u_{n-k}, v_{n-k})(y_I - v_n))$$

for $n = 0, 1, 2, \ldots$.

Convergence

Therefore the sequences u_n and v_n are well-defined and can be easily generated by the explicit delayed recurrence relations, so the solutions of the approximating equations are uniquely determined. It can be shown that

$$\lim_{h \to 0+} x_h(t) = x(t) \quad \text{and} \quad \lim_{h \to 0+} y_h(t) = y(t)$$

uniformly on each interval $[0, T]$ for any $T > 0$.

Example 1

In this example we study numerically the effect of changing the control gain for the stability of the solutions of the respiratory system. We assume normal table values except that we use $\tau = 0.25$. Furthermore, in we select $\theta_1 = 2$, $\theta_2 = 8$ for the switching times, and $G_{P1} = 45$, $G_{P2} = 60$ and $G_{P3} = 30$ for the control gains. We start the system from its equilibrium corresponding to the $G_P(t) = G_{P1}$ constant gain, i.e., use constant initial functions

$$x(t) = 41.1906, \qquad t \leq 0, \quad \text{and} \quad y(t) = 81.5645,$$

Example 1

Example 0.1 $h = 0.001$

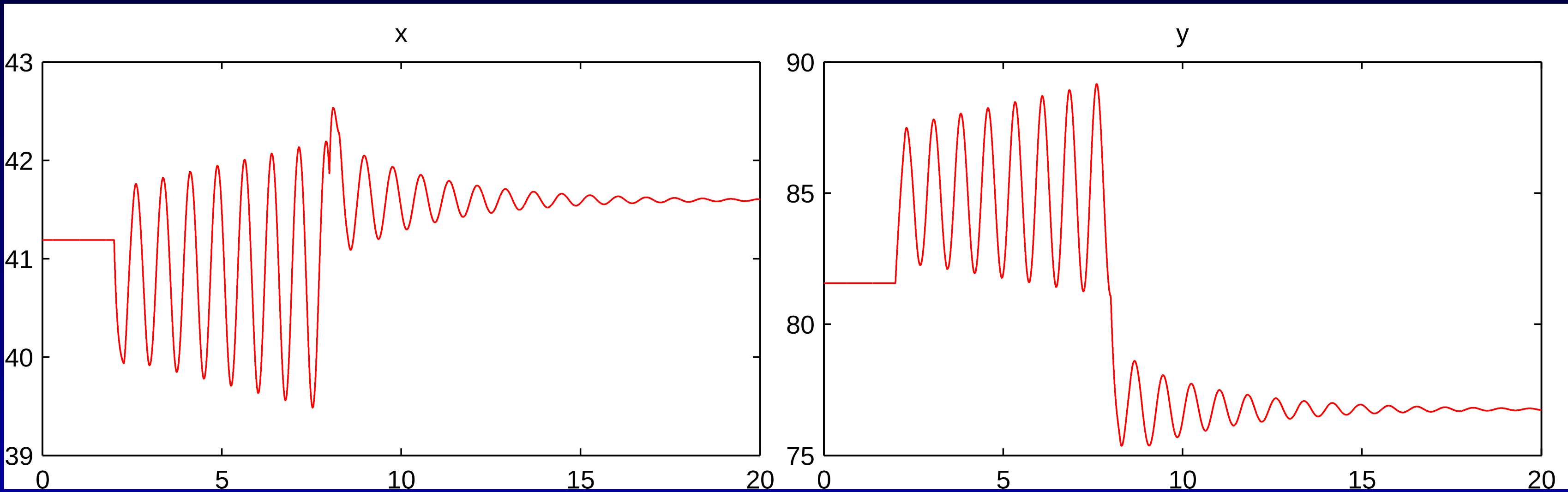

Figure 1:

We can see from the figure that the equilibrium of the system with gain $G_P(t) = G_{P2}$ is unstable, with $G_P(t) = G_{P3}$, is asymptotically stable.

Parameter Estimation

We consider again the model equations. We assume that some of the parameters in this system are not known, and we denote the unkown parameters by $\gamma_1, \ldots, \gamma_m$. We can consider, for example, the control gain constants G_{P1}, G_{P2} and G_{P3} as the unknown parameters (in that case $m = 3$ and $\gamma_i = G_{Pi}$ for $i = 1, 2, 3$), or the transport delay τ can be the only unknown parameter ($m = 1$, $\gamma_1 = \tau$), but we can consider any other parameters to be unknown.

Parameter Estimation

The goal is to determine the values of these unknown parameters, assuming we know the measurements of the solutions at finitely many times, $t_1, t_2, \ldots, t_M$. One standard approach to this problem is to define a least-square cost function, and find the parameter values with the least possible cost.

Parameter Estimation

First we need to introduce the following notation. Assume all parameters (including the initial functions) except $\gamma_1, \ldots, \gamma_m$ in the model are fixed. Then the solutions corresponding to particular selections of the parameter values $\gamma_1, \ldots, \gamma_m$ of this problem are denoted by

$$x(t; \gamma_1, \ldots, \gamma_m) \quad \text{and} \quad y(t; \gamma_1, \ldots, \gamma_m).$$

Parameter Estimation

Suppose the measurements of x and y at the time t_i are denoted by X_i and Y_i, respectively, for $i = 0, \ldots, M$. We will use equally spaced measurements over a time interval $[T_0, T]$, i.e.,

$$t_i = T_0 + \frac{T - T_0}{M} i, \qquad i = 0, 1, \ldots, M.$$

Of course, any time values could be used.

Parameter Estimation

We define the cost function by

$$J(\gamma_1, \ldots, \gamma_m) = \sum_{i=1}^{M} (x(t_i; \gamma_1, \ldots, \gamma_m) - X_i)^2$$

$$+ \sum_{i=1}^{M} (y(t_i; \gamma_1, \ldots, \gamma_m) - Y_i)^2.$$

Then the mathematical problem is to find the parameter values $\gamma_1, \ldots, \gamma_m$ which minimizes the cost function J.

Parameter Estimation

One standard approach to solve this problem is the following: find finite dimensional approximate solutions x^N, y^N of the model equations, define the corresponding cost

$$J^N(\gamma_1, \ldots, \gamma_m) = \sum_{i=1}^{M} (x^N(t_i; \gamma_1, \ldots, \gamma_m) - X_i)^2$$

$$+ \sum_{i=1}^{M} (y^N(t_i; \gamma_1, \ldots, \gamma_m) - Y_i)^2,$$

and find the minimizer $(\gamma_1^N, \ldots, \gamma_m^N)$ of J^N.

Parameter Estimation

We consider a sequence of h_N discretization constants tending to 0, and use the approximation scheme defined in the previous section corresponding to h_N as the numerical scheme in the above process. Then if N is large enough, i.e., equivalently, h_N is small enough, we find the minimizer of the corresponding cost function J^N by a a nonlinear least square minimization code, based on a secant method with Dennis-Gay-Welsch update, combined with a trust region technique.

Parameter Estimation

For the “true parameters” the value of the cost function is 0, so if the numerical method stops at a parameter value where the cost function is not close to 0, then the method is terminated at a local minimum instead of a global minimum.
Restart the method from a different initial parameter value.

The numerical method converges only locally, so we have to find a good enough initial guess of the parameters to observe convergence.

Parameter Estimation

An other practical problem in the parameter estimation problem is wether two different parameter set can generate the same measurements, i.e., the *identifiability of the parameters*. The lack of identifiability can be another reason for getting not convergent solutions.

Next, we give several numerical examples to demonstrate the applicability of the above parameter estimating process for the respiratory system. In all these examples we got good recovery of the original parameters, so we numerically observed identifiability of the considered parameters.

Example 2

In this example we generated measurements of the respiratory system corresponding to the normal parameter values and using a constant gain coefficient function $G_P(t)$, i.e.,

$$G_{P1} = G_{P2} = G_{P3} = 45.$$

We assume that the system is at the eqilibrium, so we use initial conditions $x(t) = 41.1906$ and $y(t) = 81.5645$ which correspond to the equilibrium values. The measurements are taken over the interval $[T_0, T] = [0, 2]$

Example 2

We consider the coefficients b, c, e and f to be unknown, and the goal in this example is to estimate these parameter values using the measurements. In this example we used discretization stepsize $h = 0.01$ and the initial parameters

$$b = 8.5, \qquad c = 0.3, \quad e = 0.6, \quad \text{and} \quad f = 0.4.$$

Example 2

Example 0.2

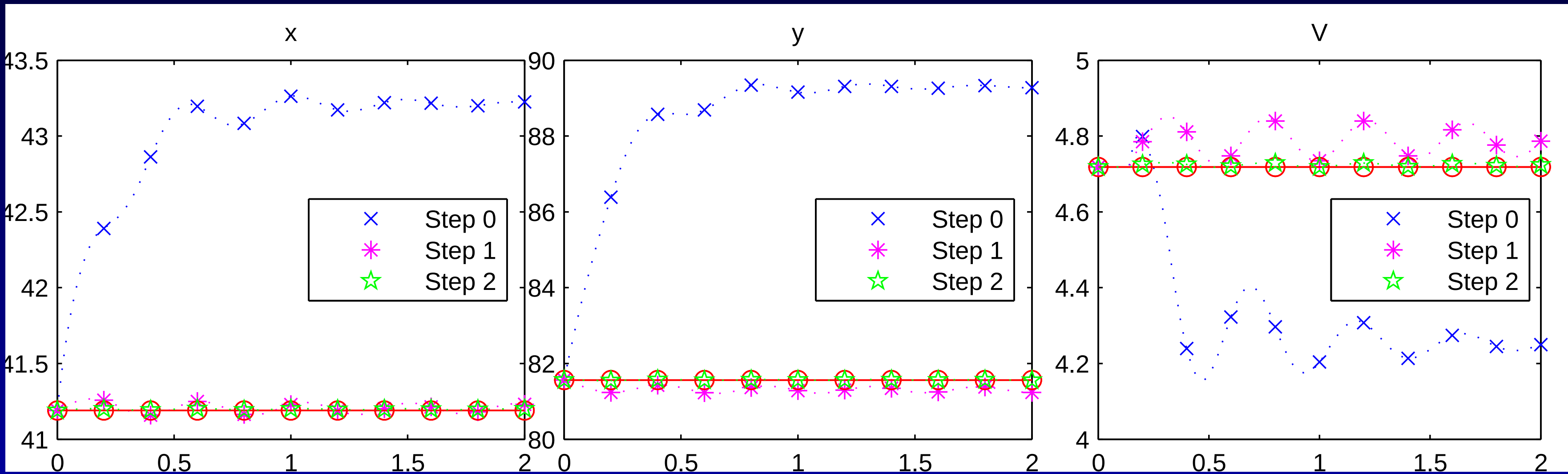

Figure 2:

The solid and dotted curves are the solutions, x, y and the ventilation function V along the solutions corresponding to the true and approximate parameter values, respectively.

Example 2

We can see that the graphs approach to the graph corresponding to the true parameter values even in the first few steps. Table 2 contains the value of the cost function, the actual parameter value. The method reaches its limit in 5 steps, but in each parameter value a small error can be observed. Our explanation for this error (which can be seen running the code from different initial values, as well) is that the constant solution is not "rich enough" for better estimation.

Example 2

Table 1: Estimation of b, c, e, f, case $G_{P1} = G_{P2} = G_{P3} = 45$

step	cost	b	c	e	f
0	287.84623772	8.50000	0.30000	0.60000	0.40000
1	0.38419648	8.80052	0.30321	0.86988	0.36664
2	0.00077480	8.81127	0.30535	0.86543	0.37275
3	0.00056159	8.81142	0.30538	0.86538	0.37282
4	0.00043748	8.81160	0.30541	0.86535	0.37287
5	0.00034371	8.81177	0.30544	0.86533	0.37290
6	0.00034371	8.81177	0.30544	0.86533	0.37290

Example 3

In this example we change the gain constants in the wentilation to move the solutions away from the equilibrium. We use switching times $\theta_1 = 0.2$ and $\theta_2 = 0.4$ and gain constants

$$G_{P1} = 45, \quad G_{P2} = 0, \quad G_{P3} = 60.$$

This corresponds to the situation when one takes normal breaths, then stops breathing for 12 seconds (between time 0.2 and 0.4 minutes), but then takes larger breaths for a while. We again try to estimate b, c, e and f. We used the same initial parameter values, measurements and $h = 0.01$ as in Example 2.

Example 3

Example 0.3

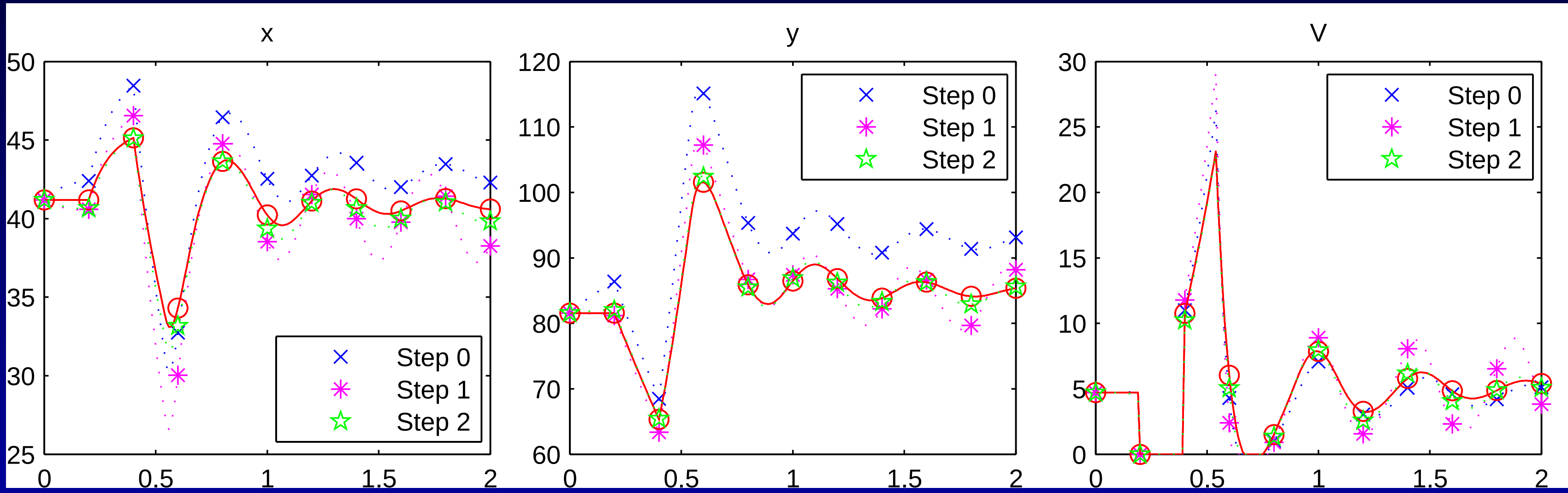

Figure 3:

Example 3

Table 2: Estimation of b, c, e, f, case $G_{P1} = 45$, $G_{P2} = 0$, $G_{P3} = 60$

step	cost	b	c	e	f
0	350.31169443	8.50000	0.30000	0.60000	0.40000
1	51.72675038	8.86517	0.33654	0.63847	0.30804
2	3.54921161	9.21149	0.25766	0.53943	0.29705
3	0.00525638	9.21676	0.22070	0.51609	0.27984
4	0.00000009	9.22328	0.21876	0.51779	0.28000
5	0.00000000	9.22330	0.21875	0.51780	0.28000

Example 4

Now we use the same meaurements and $h = 0.01$ as in Example 3, but now we consider G_{P1}, G_{P2} and G_{P3} as the unknown parameters in the system. (The switching times are the same as in the previous example.) Starting from the $G_{P1} = G_{P2} = G_{P3} = 40$ initial guess, we again get good approximation of the true parameters, as can be seen in Figure 4 and in Table 4.

Example 4

Example 0.4

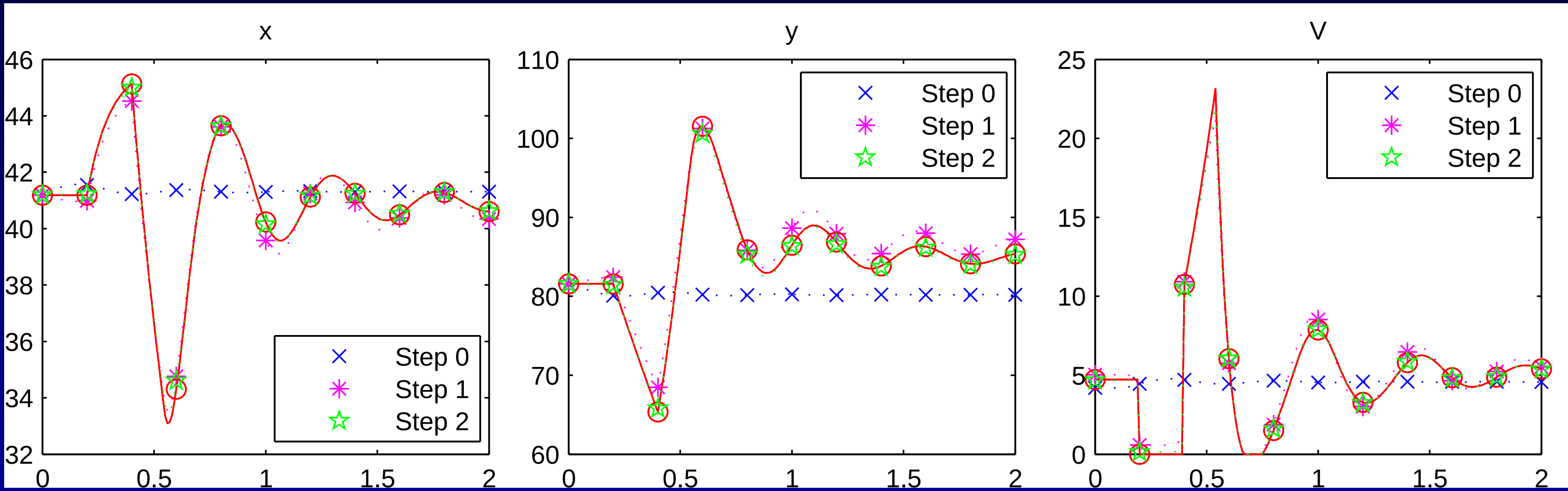

Figure 4:

Example 4

Table 3: Estimation of G_{P1}, G_{P2} and G_{P3}

step	cost	G_{P1}	G_{P2}	G_{P3}
0	483.75379438	40.00000	40.00000	40.00000
1	14.01499742	47.97180	5.86922	68.70514
2	0.90980645	44.53413	1.28130	59.25469
3	0.04368879	45.07905	0.28985	59.98344
4	0.03010176	44.99316	0.28580	60.00549
5	0.01160245	44.80199	0.28644	60.08301
6	0.01160203	44.80199	0.28644	60.08302

Example 5

In this example we repeat the previous experiment with the only difference that in the measurements of x and y there is a random error of normal distribution with absolute value less than 0.3. The corresponding numerical results can be seen in Figure **??** and in Table **??**. With this noisy measurements the numerical result is also convergent, but we can observe larger error (in G_{P1} and G_{P3} than in the previous example.

Example 5

Example 0.5

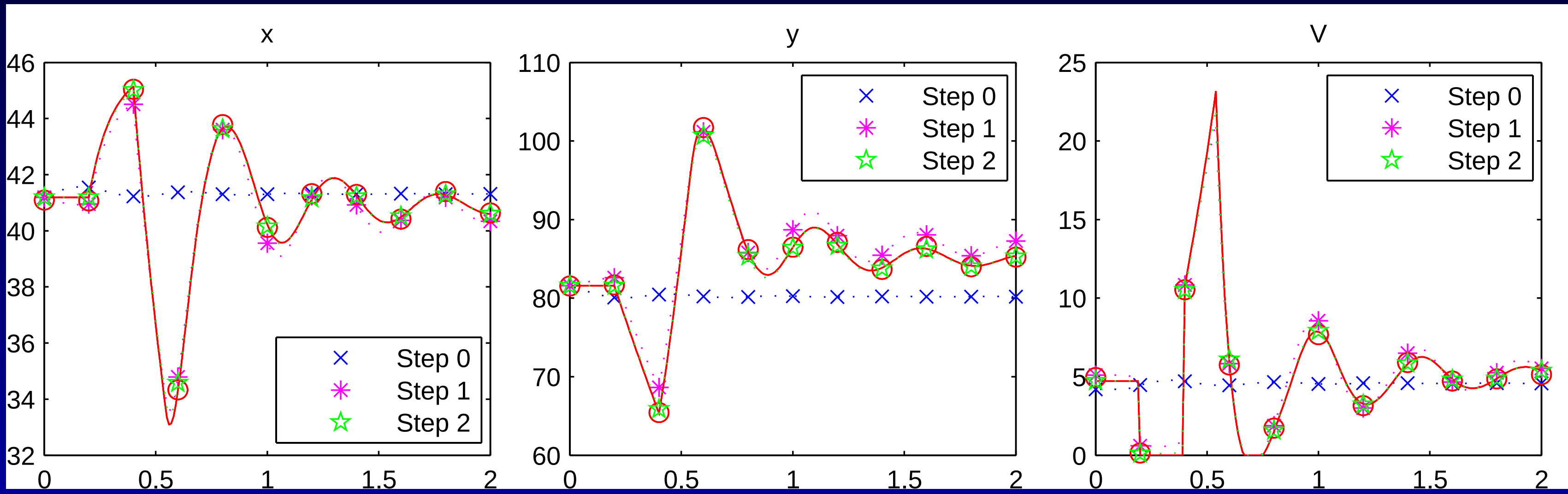

Figure 5:

Example 5

Table 4: Estimation of G_{P1}, G_{P2} and G_{P3} using noisy measurements of x and y

step	cost	G_{P1}	G_{P2}	G_{P3}
0	485.59595635	40.00000	40.00000	40.00000
1	14.52482670	47.17405	5.54416	68.35639
2	1.15085189	43.70021	1.16266	58.68728
3	0.24101584	44.26992	0.20717	59.44590
4	0.22474717	44.17809	0.20403	59.46826
5	0.20156319	43.98286	0.20541	59.55063
6	0.20156185	43.98286	0.20541	59.55066

Example 6

In this example we assume that we do not have direct measurements of the solutions x and y, instead, we suppose we can measure the value of the ventilation function along the solution. Let $\bar{G}_{P1}, \bar{G}_{P3}, \bar{G}_{P3}$ denote the true parameters,

$$V_i = V(t_i, x(t_i; \bar{G}), y(t_i; \bar{G})), \qquad i = 0, 1, \ldots, M,$$

and now we use the following cost function

$$\tilde{J}(G) = \sum_{i=0}^{M} (V(t_i, x(t_i; G), y(t_i; G)) - V_i)^2.$$

Example 6

Example 0.6

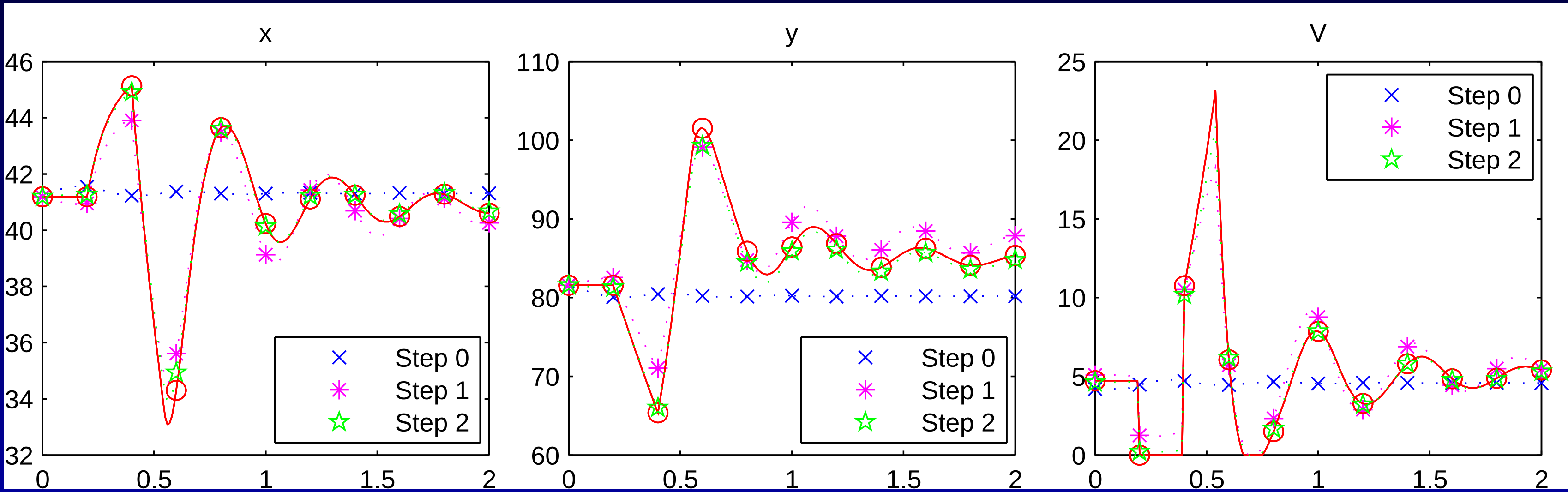

Figure 6:

Example 6

Table 5: Estimation of G_{P1}, G_{P2} and G_{P3} using measurements of V

step	cost	G_{P1}	G_{P2}	G_{P3}
0	42.10899178	40.00000	40.00000	40.00000
1	2.63937045	48.52067	12.50361	71.69544
2	0.22630530	44.09782	2.03095	57.15278
3	0.00867380	45.50737	0.13858	60.12323
4	0.00443630	45.31892	0.13395	60.05083
5	0.00044917	45.01624	0.13081	59.99976
6	0.00025245	44.95685	0.12889	60.00478

Example 7

We repeat the previous experiment but adding a random error of normal distribution with absolute value less than 0.3 to the measurements of V used in the previous example. With this noisy measurements the numerical result is also convergent, but the convergence was very slow in this case. We listed only the first 7 steps of the numerical results in Table 7, and the first two iterates in Figure 7. We can observe larger error than in the previous example.

Example 7

Example 0.7

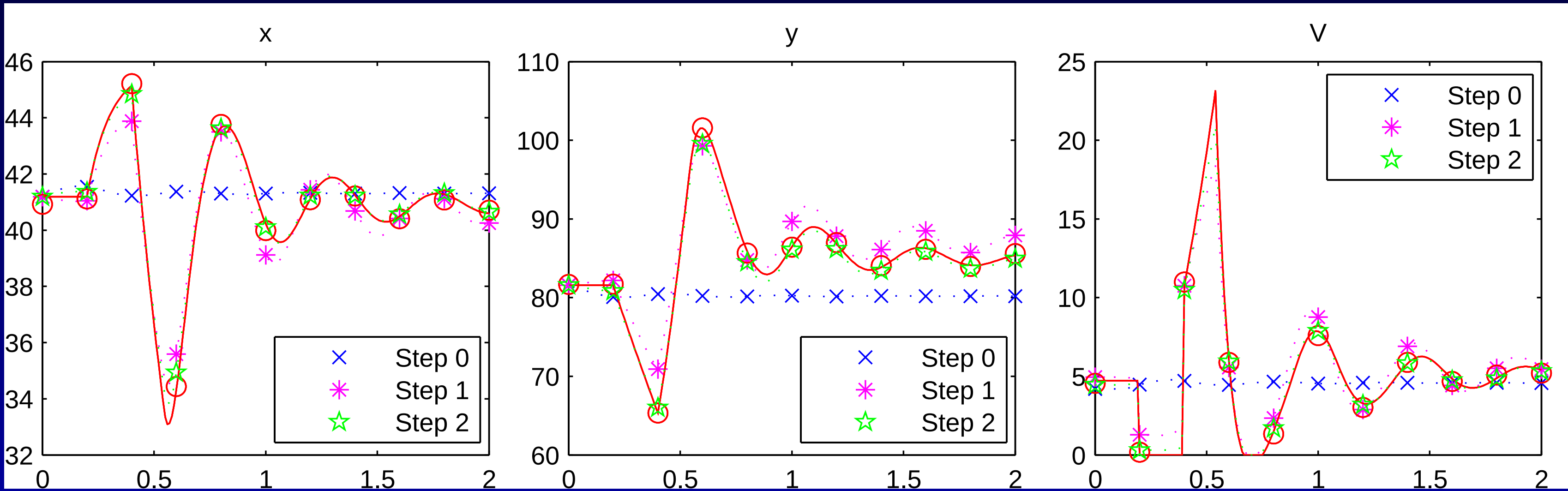

Figure 7:

Example 7

Table 6: Estimation of G_{P1}, G_{P2} and G_{P3} using noisy measurements of V

step	cost	G_{P1}	G_{P2}	G_{P3}
0	41.06549791	40.00000	40.00000	40.00000
1	2.69930168	47.91054	12.67821	71.49751
2	0.26392223	43.53271	2.32477	56.08888
3	0.10162997	43.60376	0.87665	57.97591
4	0.10161041	43.59960	0.87671	57.97828
5	0.10148228	43.54956	0.88325	57.97853
6	0.10142830	43.52050	0.89136	57.96415
7	0.10135694	43.47035	0.90820	57.93390

Example 8

In this example we assume that the transport delay τ is the only unknown parameter. If we start the system from its equilibrium, then changing the time delay has no effect on the solution, therefore it is not possible to identify the delay from such measurement. Therefore it is necessary to move away the system from the equilibrium. For this we again use the gain function is defined by the parameters

$$\theta_1 = 0.2, \quad \theta_2 = 0.4, \quad G_{P1} = 45, \quad G_{P2} = 0, \quad G_{P3}$$

Example 8

We also observed that if we use measurements on the interval where the solution is still constant, i.e., on $[0, 0.2]$, then at these points the solution again does not depend on the delay, and the numerical minimization method will not usually converge. Therefore now we used the interval $[T_0, T] = [0.3, 2]$ to make measurements using equidistant time points with $M = 11$. Starting from $\tau = 0.25$ and using $h = 0.0005$ we got a convergent sequence, what can be seen in Figure 8 and in Table 8.

Example 8

We get again a very good approximation of the original delay value, $\tau = 0.1417$. In this experiment the convergence of the scheme is sensitive for the selection of the initial parameter value. The reason of it is that if at any step the numerical scheme produces a “large” τ, then using that τ the corresponding solution will be constant on $[0.3, 1]$, therefore the minimization will fail. Also, in identifying the delay the discretization constant has to be very small, since otherwise small change in the delay has no effect on the approximate solution, so the minimization will fail.

Example 8

Example 0.8

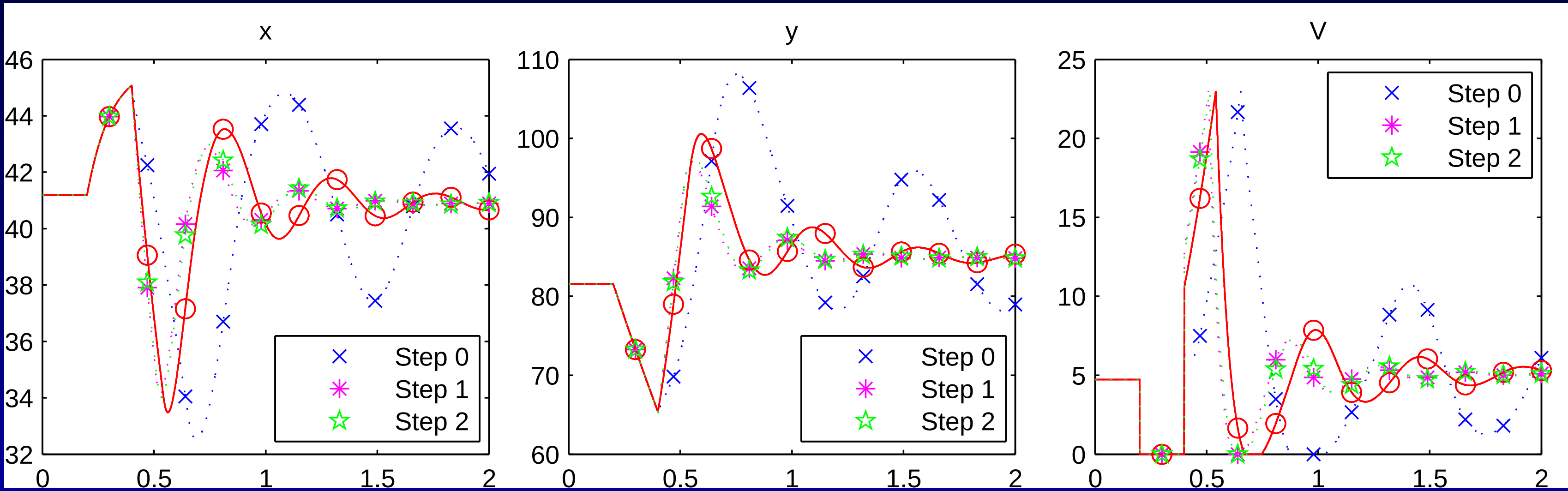

Figure 8:

Example 8

Table 7: Estimation of τ

step	cost	τ	$\Delta(\tau)$
0	458.59350832	0.25000	0.10830
1	53.96078682	0.10704	0.03466
2	42.51290806	0.11226	0.02944
3	20.15586956	0.12306	0.01864
4	0.29816598	0.14364	0.00194
5	0.00000000	0.14178	0.00008

Conclusions

Information rich data helps the identification process.
Identifiability of the parameters was observed numerically.
Simulations were done assuming ventilation, O_2, CO_2 measurements. Question what can be done more accurately?

Numerical study can be extended to more sophisticated models.

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